Treatment of Proximal Deep Vein Thrombosis With a Novel Synthetic Compound (SR90107A/ORG31540) With Pure Anti–Factor Xa Activity

A Phase II Evaluation

The Rembrandt Investigators*

Background—Patients with venous thromboembolism require initial treatment with an immediate-acting anticoagulant, low-molecular-weight heparin. We evaluated a novel synthetic factor Xa inhibitor (SR90107a/ORG31540) as an alternative treatment.

Methods and Results—A randomized-parallel-group, phase II trial to assess the efficacy and safety of SR90107a/ORG31540 (5, 7.5, or 10 mg once daily) relative to low-molecular-weight heparin (dalteparin, 100 IU/kg twice daily) in symptomatic proximal deep vein thrombosis. The primary outcome measure was the change in thrombus mass, assessed by ultrasonography of the leg veins and perfusion lung scintigraphy, performed at baseline and day 7±1. A positive outcome was defined as improvement of the ultrasound and/or perfusion scan result without deterioration of either test. Other outcome measures included symptomatic, recurrent venous thromboembolism and major bleeding for a period of 3 months. All outcomes were interpreted with the observer unaware of treatment allocation. A positive primary outcome was observed in 46 of 100 (46%), 52 of 108 (48%), 48 of 115 (42%), and 56 of 115 (49%), respectively, of the subjects given 5, 7.5, or 10 mg SR90107a/ORG31540 or dalteparin. There were 8 recurrent thromboembolic complications (2.4%) in the 334 patients treated with SR90107a/ORG31540 and 6 (5.0%) in the 119 dalteparin patients, a difference of 2.6% in favor of SR90107a/ORG31540 (95% CI −2.1% to 10.1%). The incidence of bleeding was low and was similar among the groups.

Conclusions—The factor Xa inhibitor SR90107a/ORG31540 appears to be an effective and safe treatment for patients with deep vein thrombosis across a wide range of doses. This synthetic compound merits evaluation in phase III studies. **(*Circulation*. 2000;102:2726-2731.)**

Key Words: anticoagulants ■ heparin ■ imaging ■ thrombosis

Current management of patients with acute venous thromboembolism requires initial treatment with an immediate-acting antithrombotic drug to prevent thrombus extension and/or embolization.[1]

For this purpose, ≈1 week of either unfractionated heparin or low-molecular-weight heparin is the accepted initial treatment. Both compounds work through antithrombin, although they differ in their ratios of anti–factor Xa to anti–factor IIa activity. Definitive evidence for the effectiveness of these treatments has come from large randomized trials using clinical outcomes.[1–3]

SR90107a/ORG31540 is a synthetic pentasaccharide[4] (Figure 1). It selectively binds to antithrombin and induces a conformational change that increases the anti–factor Xa activity of antithrombin >270 times, without inhibition of factor IIa.[5] In early studies, SR90107a/ORG31540 has been shown to be safe and effective in preventing thrombus formation in hemodialysis circuits. In addition, this compound inhibits thrombus extension in animal studies.[6] These findings suggest that the new compound has the potential to be effective not only for the prevention but also for the treatment of venous thromboembolism. Its long half-life of ≈18 hours makes it suitable for once-daily administration. In addition, this factor Xa inhibitor shows no cross-reactivity with antibodies associated with heparin-induced thrombocytopenia, and the product is synthetic and not of animal origin.[7]

It is generally believed that independent of the type of heparin, a significant amount of thrombin inhibition is crucial for achieving antithrombotic effectiveness.[8] Hence, the confirmation that a pure factor Xa inhibitor is effective would challenge current concepts that thrombin is pivotal for mediating thrombus propagation.

This randomized study in patients with symptomatic acute proximal deep vein thrombosis was designed to investigate

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*A list of all the Rembrant Investigators is given in the Appendix. Note: Drs Büller, Prins, Gent, Ginsberg, and Gallus (members of the Rembrandt Executive Committee) serve as advisors to both Sanofi and Organon; Dr Cariou is an employee of Sanofi, Paris, France.

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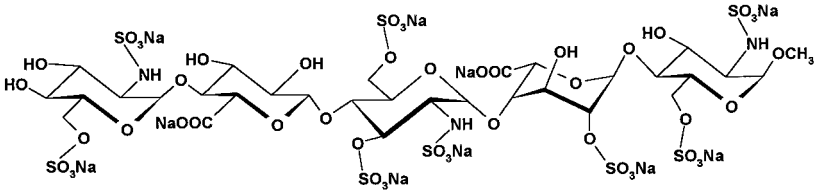

Chemical structure of SR90107a/ORG31540.

the relative efficacy and safety of 3 doses of SR90107a/ORG31540 compared with low-molecular-weight heparin to select an appropriate dose for further evaluation in phase III studies. We therefore compared the thrombotic burden before and after 1 week of treatment, as observed with repeated ultrasonography and perfusion lung scanning. Similar measures of early subclinical thrombus evolution have been shown to correlate with clinical events during long-term follow-up.[9]

Methods

Study Patients

Consecutive patients with acute, symptomatic proximal deep vein thrombosis who were ≥18 years old were eligible for the study. The diagnosis had to be documented by compression ultrasonography. Patients were ineligible if they had symptomatic pulmonary embolism; previously documented thrombosis in the same leg, unless complete ultrasound normalization had been documented; a known bleeding tendency; surgery within the previous 5 days; a body weight of <50 kg or >100 kg; or any contraindication for anticoagulant treatment. Other reasons for exclusion included treatment with therapeutic dosages of anticoagulants for >24 hours before randomization; a documented pregnancy or being of childbearing potential without adequate contraception; drug-addictive disorder or alcoholism; known renal insufficiency; a life expectancy of <6 months; and participation in another clinical drug study within the previous 90 days. After informed consent was given, randomization was performed by use of a computer algorithm through a central 24-hour telephone service. Specific information on the patient was recorded before the treatment assignment was disclosed. The study protocol was approved by all institutional review boards.

Treatment Regimens

Patients were randomly assigned to parallel groups receiving any 1 of 3 dosages (5, 7.5, or 10 mg once daily), without body weight adjustment, of SR90107a/ORG31540 (Sanofi; Organon) or 100 IU/kg twice daily of the low-molecular-weight heparin dalteparin sodium (Pharmacia-Upjohn). The choice of 5 mg as the lowest dose was based on results from phase II studies in the prevention of postoperative thrombosis (unpublished data) and pharmacokinetic data. The highest dose was selected because repeated injection of 12 mg once daily caused minor bleeding in healthy volunteers.[10] Patients randomized to SR90107a/ORG31540 received a once-daily subcutaneous injection of this compound and a twice-daily subcutaneous injection of a placebo matching dalteparin. Patients randomized to dalteparin received a once-daily subcutaneous injection of a placebo matching pentasaccharide and a twice-daily subcutaneous injection of dalteparin. The volumes of the syringes with SR90107a/ORG31540 or its matching placebo had to be adjusted to obtain the correct dose. No laboratory monitoring was used, and no dose adjustments of study drug were made. Treatment with vitamin K antagonists was started on day 1 or 2 and continued for ≥90 days. Prothrombin times were initially measured at least every other day, and the dose was adjusted to achieve an international normalized ratio (INR) between 2.0 and 3.0. The study drug was discontinued when the INR was maintained at ≥2.0 for 2 consecutive days and the patient had received study drug for ≥5 days. The use of therapeutic dosages of unfractionated or low-molecular-weight heparin was allowed, provided that it was stopped 2 or 6 hours, respectively, before randomization and given for <24 hours.

During study drug administration, other antithrombotic agents were prohibited.

Primary Outcome Assessment

The primary outcome measure was the change in thrombus mass as assessed by ultrasonography of the affected limb(s) in combination perfusion lung scintigraphy, both performed at baseline and again on day 7±1. The diameter of the popliteal and common femoral veins at full compression and the precise anatomic location were recorded. A change in diameter of >2.0 mm was considered an improvement or a worsening. Six-view perfusion lung scans were obtained, and the defects were scored by use of an anatomic reference chart.[11,12] With this score, each lobe is assigned a weight based on the regional distribution of pulmonary blood flow. An estimation of remaining perfusion is made for each lobe from 0.0 (no perfusion), to 0.25, 0.50, 0.75, to 1.0 (normal perfusion). The total perfusion score is the sum of the remaining perfusion multiplied by the assigned weight of the 6 lobes. The respective findings of improved, unchanged, or deteriorated for each test were combined into a single, binary result. For this purpose, a positive outcome was defined as an improvement on ultrasound and/or perfusion without deterioration of either test. All other combinations were considered negative outcomes. All tests were interpreted by an Independent Central Adjudication Committee unaware of treatment allocation. The results of the repeat lung scan and ultrasonography did not influence subsequent treatment in asymptomatic patients.

Clinical Outcome Assessment

All patients were contacted daily during the initial treatment and again after 6 and 12 weeks to elicit whether they had experienced signs or symptoms of recurrent venous thromboembolism or bleeding. Patients were instructed to report to the center immediately if such symptoms developed. Confirmatory testing was necessary to document the presence of a recurrence. The collected information on potential recurrences and bleeding episodes was reviewed by the Independent Central Adjudication Committee. Also, all deaths were reviewed to assess the likelihood of pulmonary embolism or bleeding being the cause of death.

Recurrent thromboembolism was defined as symptomatic and objectively documented extension or recurrence of deep vein thrombosis or the occurrence of symptomatic pulmonary embolism, according to criteria reported earlier.[2,3]

Major bleeding was defined as clinically overt and associated with a fall in hemoglobin level >2 g/dL or leading to a transfusion of ≥2 units of red cells; if it was intracranial, retroperitoneal, or in a critical organ; or when it was fatal. Minor bleeding was defined as clinically unusual overt bleeding not meeting the criteria for major bleeding.

Episodes of recurrent venous thromboembolism or major bleeding, as well as deaths, were assigned to period 1 if they occurred during study drug administration or within 48 hours of its cessation. Events occurring thereafter were assigned to period 2.

Laboratory Analysis

Plasma concentrations of SR90107a/ORG31540 were determined in a core laboratory by an inhibition assay. Briefly, residual factor Xa activity was measured with a chromogenic substrate in diluted plasma samples after addition of a known quantity of factor Xa and an excess of purified antithrombin. The concentration of SR90107a/ORG31540 is expressed relative to the pretreatment value in mg/L.

TABLE 1. Baseline Characteristics of the Intention-to-Treat Cohort

Characteristic	SR90107a/ORG31540 5 mg (n=103)	SR90107a/ORG31540 7.5 mg (n=111)	SR90107a/ORG31540 10 mg (n=120)	Dalteparin (n=119)
Clinical characteristics				
Mean age, y (SD)	61.7 (17.6)	57.8 (18.9)	59.6 (16.4)	64.4 (16.0)
Mean BMI, kg/m^2 (SD)	26.1 (3.9)	26.2 (4.7)	26.5 (4.4)	26.5 (3.6)
Median duration of DVT symptoms, d (range)	5 (0 to 41)	4 (0 to 51)	4 (0 to 62)	5 (0 to 45)
Male sex, n (%)	49 (47.6)	57 (51.4)	68 (56.7)	59 (49.6)
Active cancer, n (%)	11 (10.7)	12 (10.8)	16 (13.3)	15 (12.6)
Previous venous thromboembolism, n (%)	35 (34.0)	29 (26.1)	29 (24.2)	30 (25.2)
Surgery in the previous 3 months, n (%)	21 (20.4)	22 (19.8)	21 (17.5)	27 (22.7)

BMI indicates body mass index; DVT, deep-vein thrombosis.

Statistical Analysis

The primary analysis of efficacy was performed in a per-protocol cohort, whereas the remaining analyses included all patients who received ≥1 dose of study drug (intention-to-treat cohort). Patients were included in the per-protocol analysis if they had confirmed symptomatic deep vein thrombosis at entry, if they had a primary efficacy outcome available done between days 6 and 8 unless there was an earlier symptomatic recurrence, if they had received study drug for ≥5 days, and if they did not use any prohibited medication.

It was calculated that a sample size of 100 patients per group in the per-protocol cohort would detect a 25% absolute difference in positive outcome rates between treatment groups (type I error of 0.05, 2-sided; type II error of 0.05).

Dose effects were determined by tests for trend. Frequencies of outcomes were compared between groups of patients receiving SR90107a/ORG31540 or dalteparin, and 95% CIs of the differences were calculated. In addition, a comparison was planned between the combined SR90107a/ORG31540 group with the patients receiving dalteparin. For the comparisons among subgroups, the χ^2 test (2-sided) was used. In addition, odds ratios and their corresponding 95% CIs were calculated where indicated.

Results

Study Patients

Recruitment started in March 1997, and follow-up was completed in August 1998. Of 456 patients who were randomized, 3 did not receive study drug and were excluded from further analyses. The baseline characteristics of the patients in the 4 treatment groups are shown in Table 1. The thrombotic burden measurements at entry of the 438 patients who had an adequate primary efficacy outcome assessment are summarized in Table 2.

An additional 57 patients (12.6%) were excluded from the per-protocol analysis for the following reasons (some had >1 reason): use of prohibited treatment (n=27); primary outcome assessment performed outside the permissible time window (n=16); no adequate lung scan or ultrasound evaluation available (n=15); <5 days of study drug (n=8); or incorrect dose of study medication (n= 3). Thus, 396 patients were included in the per-protocol analysis. Their baseline demographic and clinical characteristics as well as their thrombotic burden were similar to those of the intention-to-treat cohort (data not shown).

Treatment and Follow-Up

Data on the initial treatment are given in Table 3. A total of 16 patients (3.5%) discontinued study drug early for the following reasons: suspected recurrent venous thromboembolism (n=5); protocol violations (n=4); withdrawal of consent (n=4); or the occurrence of adverse events (n=3). No patient was lost to follow-up.

Primary Efficacy Outcome

The results of the primary efficacy assessment were similar for the per-protocol and intention-to-treat cohorts. In the

TABLE 2. Thrombotic Burden at Presentation in the Intention-to-Treat Cohort

Characteristic	SR90107a/ORG31540 5 mg (n=103)	SR90107a/ORG31540 7.5 mg (n=111)	SR90107a/ORG31540 10 mg (n=120)	Dalteparin (n=119)
No outcome assessment available, n	3	3	5	4
Available for analysis, n	100	108	115	115
Bilateral DVT, n (%)	6 (6.0)	3 (2.8)	4 (3.5)	9 (7.8)
DVT location, n (%)				
Femoral	49 (49.5)	52 (48.1)	52 (45.6)	48 (41.7)
Popliteal only	50 (50.5)	56 (51.9)	62 (54.4)	67 (58.3)
Mean sum diameter of thrombus on ultrasound, mm (SD)	12.6 (6.7)	11.3 (5.7)	11.1 (5.5)	12.2 (6.2)
Abnormal perfusion scan at entry, n (%)	84 (84.0)	96 (88.9)	83 (72.2)	101 (87.8)

DVT indicates deep-vein thrombosis.

TABLE 3. Details on Initial Treatment of All Patients

	SR90107a/ORG31540			
	5 mg (n=103)	7.5 mg (n=111)	10 mg (n=120)	Dalteparin (n=119)
Mean duration of study drug, d (SD)	6.7 (1.5)	6.6 (1.3)	6.8 (1.6)	6.9 (1.5)
Mean AUC of SR90107a/ORG31540, $mg \cdot h \cdot L^{-1}$ (SD)	15.1 (6.07)	19.7 (7.71)	22.9 (5.23)	...
Early discontinuation of study drug, n (%)	3 (2.9)	2 (1.8)	6 (5.0)	5 (4.2)
INR at discontinuation of study drug (SD)	2.9 (0.7)	2.9 (1.0)	2.9 (0.8)	2.7 (0.6)

AUC indicates area under the curve as determined in steady state (day 4).

interest of consistency in data presentation, Table 4 summarizes the results for the intention-to-treat cohort. All 3 doses of the factor Xa inhibitor were as effective as dalteparin and not significantly different from each other. Overall, 146 (45.2%) of the patients receiving the new compound had a positive outcome, compared with 56 (48.7%) in the dalteparin group (absolute difference 3.5%; 95% CI −7.2% to 15.0%). In the per-protocol cohort, 134 (46.4%) of the 289 patients receiving SR90107a/ORG31540 had a positive outcome, compared with 50 of 107 (46.7%) in the dalteparin group (absolute difference 0.3%; 95% CI −10.8% to 12.4%).

Clinical Outcomes

As shown in Table 5, there were 14 symptomatic and confirmed recurrent thromboembolic complications in the entire study cohort, with comparable rates in the 3 dosage groups. Eight (2.4%) were observed in the 334 patients treated with SR90107a/ORG31540 and 6 (5.0%) in the 119 patients receiving dalteparin (difference 2.6% in favor of the SR90107a/ORG31540; 95% CI −2.1% to 10.1%). Six of the 14 recurrent events were pulmonary emboli, of which 3 occurred in the dalteparin group and 3 in the group that received 10 mg of SR90107a/ORG31540. Only 4 patients had a recurrent event during initial treatment (2 in the dalteparin and 2 in the 5 mg SR90107a/ORG31540 group).

Overall, the incidence of major bleeding was low and not significantly different among the treatment groups. Of the 6 major bleeds that occurred during initial treatment, 4 occurred at the sites of malignant lesions and 1 in the presence of an INR of 4.7. The other major bleed was a large muscular hematoma at an injection site in a patient in the 10 mg SR90107a/ORG31540 group.

During the entire study period, 24 patients (5.3%) died. Of these, had 15 received the synthetic factor Xa inhibitor (4.5%) and 9 dalteparin (7.6%). No deaths occurred during the initial treatment period, nor was the cause of any of the deaths adjudicated as pulmonary embolism or hemorrhage. Fifteen of the deaths (27.8% of 54 patients) occurred in the 54 patients with active cancer at entry.

Additional Observations

There appeared to be a relationship between clinical events and the changes observed on the repeat ultrasound and perfusion scans. Fourteen of the 438 patients with an evaluable primary efficacy outcome assessment had a symptomatic and objectively confirmed recurrent venous thromboembolic event. Of these, 6 (9.5%) occurred among the 63 patients with worsening ultrasonography and/or perfusion lung scan, whereas 8 (2.1%) occurred in the 375 patients without a worsening of these tests (OR 4.8, 95% CI 1.61 to 14.3, $P<0.005$).

Discussion

This clinical trial evaluating 3 doses of the synthetic factor Xa inhibitor SR90107a/ORG31540 suggests that this compound

TABLE 4. Results of Primary Efficacy Outcome in the Intention-to-Treat Cohort With an Outcome Assessment

	SR90107a/ORG31540			
Outcome Status	5 mg (n=103)	7.5 mg (n=111)	10 mg (n=120)	Dalteparin (n=119)
No outcome assessment available	3	3	5	4
Available for analysis	100	108	115	115
All negative outcome	54 (54.0)	56 (51.9)	67 (58.3)	59 (51.3)
Worsening US	6 (6.0)	5 (4.6)	6 (5.2)	4 (3.5)
Worsening PLS	13 (13.0)	8 (7.4)	11 (9.6)	13 (11.3)
Unchanged US/PLS	38 (38.0)	43 (39.8)	50 (43.5)	42 (36.5)
Positive outcome	46 (46.0)	52 (48.1)	48 (41.7)	56 (48.7)
Improved US	26 (26.0)	23 (21.3)	27 (23.5)	30 (26.1)
Improved PLS	28 (28.0)	45 (41.7)	33 (28.7)	35 (30.4)

US indicates ultrasound; PLS, perfusion lung scan. In 3 patients, worsening of both US and PLS occurred. Patients can have an improvement in both US and PLS. Values are number of patients (%).

TABLE 5. Clinical Outcomes in the Intention-to-Treat Cohort

Type of Outcome	SR90107a/ORG31540 5 mg (n=103)	SR90107a/ORG31540 7.5 mg (n=111)	SR90107a/ORG31540 10 mg (n=120)	Dalteparin (n=119)
Recurrent VTE				
Period 1	2	0	0	2
Period 2	0	2	4	4
Entire study	2 (1.9)	2 (1.8)	4 (3.3)	6 (5.0)
All bleeding				
Period 1	8	9	6	13
Period 2	3	10	2	8
Entire study	10 (9.7)	16 (14.4)	8 (6.7)	20 (16.8)
Major bleeding				
Period 1	3	2	1	0
Period 2	1	0	0	3
Entire study	4 (3.9)	2 (1.8)	1 (0.8)	3 (2.5)
Death				
Period 1	0	0	0	0
Period 2	6	6	3	9
Entire study	6 (5.8)	6 (5.4)	3 (2.5)	9 (7.6)

VTE indicates venous thromboembolism. Some patients had minor bleeding during both periods. Period 1 is defined as the period of study drug administration plus 2 calendar days; period 2 is defined as the period following period 1 until end of follow-up (day 42). Values are number of patients (%).

is an effective and safe treatment for patients with acute symptomatic proximal deep vein thrombosis.

The major purpose of this trial was to select an appropriate dose of SR90107a/ORG31540 for further evaluation in phase III studies. The incidence of recurrent thromboembolism and major bleeding was low in all SR90107a/ORG31540 groups. Although this study was not designed primarily to compare clinical outcomes, it is of interest to note the 95% CI for the absolute difference in the recurrent rates of symptomatic and confirmed venous thromboembolism. For the combined SR90107a/ORG31540 groups in comparison to dalteparin, this was −2.1% to 10.1%. This indicates that the risk of recurrence with SR90107a/ORG31540 is unlikely to be >2.1% greater than that with dalteparin, which would conventionally indicate that there is at least clinical equivalence.[3]

In this phase II study, another objective was to demonstrate a dose-response relationship, which was not observed, although there was a clear dose response for the SR90107a/ORG31540 plasma concentrations (Table 3). Because the consequences of undertreating thrombosis are thrombus extension and pulmonary embolism and the penalty for overdose is bleeding, when designing this study we deliberately chose to restrict the dose range to be evaluated to 5 to 10 mg/d. The choice was based on available information that suggested that this range would not jeopardize the safety of patients participating in the study.

Although no statistically significant evidence of dose-response relationship was found within this range, small differences among the groups cannot be excluded. In support of this possibility, the only 2 patients with a recurrence during SR90107a/ORG31540 treatment received the lowest dose, whereas the only unusual major bleeding episode occurred in a patient given the highest SR90107a/ORG31540 dose. After consideration of all of the available information, including the frequency of worsening of perfusion lung scanning and ultrasonography, the dose of 7.5 mg/d appears to be appropriate for further evaluation.

The results of this study challenge the dogma that only agents that inhibit thrombin are effective antithrombotics. It has been postulated that clot-bound thrombin is predominantly responsible for causing thrombus growth by 2 mechanisms.[4] The first is cleavage of fibrinogen by clot-bound thrombin, and the second is autocatalysis of thrombin through feedback activation of factors V, VIII, and XI.[4] Of these, feedback loops are thought to be the more important. Because SR90107a/ORG31540 has only anti–factor Xa activity and is not expected to inhibit thrombin bound to fibrin, the findings of this trial lead us to hypothesize that blocking further thrombin generation by inhibiting feedback loops is an effective way of preventing thrombus growth. This hypothesis is further supported by observations from animal experiments with recombinant tick anticoagulant protein, another factor Xa inhibitor.

A novel aspect of this trial is the systematic and combined use of perfusion lung scanning and venous ultrasonography for primary outcome assessment. This approach, which is based on previous experience with repeated venography and lung scanning, avoids the hazards and higher costs of venography.[9] Its clinical validity is supported by our finding of a significantly higher rate of subsequent symptomatic events among patients with early subclinical thrombus extension or embolism. Hence, we believe that this noninvasive approach is a valuable tool for evaluating new antithrombotic strategies in venous thromboembolism.

It is important to address some potential limitations of our study. As in other clinical trials of anticoagulant therapy, patients with a high perceived risk of bleeding were excluded. Otherwise, the study sample was representative of patients with deep vein thrombosis with regard to clinical characteristics and the risk of recurrent thromboembolism. Study drug administration was veiled, ie, the dose but not the type of drug was known to the investigator and patient. However, the potential for bias was minimized by use of central randomized treatment allocation and a blinded assessment of outcomes by an Independent Adjudication Committee.

To summarize, the results of our study indicate that SR90107a/ORG31540 is a safe and effective treatment for patients with proximal deep vein thrombosis and merits further evaluation in phase III studies. In addition, this new compound is fully synthetic, does not cross-react with antibodies against heparin–platelet factor 4 complexes,[7] and is consequently unlikely to induce thrombocytopenia.

Appendix

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